has now issued as U.S. Patent No. 5,344,754, reference to the patent no. has been substituted. Applicants wish to point out that reference to these then pending applications was intended as part of their duty of disclosure. As the inventorship on the present application is different than those on the copending applications, these applications are available as prior art under 35 USC §102(e) when they issue. While the disclosures were incorporated by reference, it is not believed that any of the information in either of the applications was essential.

A new abstract of the disclosure has been introduced which overcomes the objections of the Examiner.

A new title has been introduced which is believed to be clearly indicative of the invention to which the claims are directed.

Finally, the full citation to reference A5 is as follows: "Biochemistry" J. David Rawn, 1989, Neil Patterson Publishers, Carolina Biological Supply Co., Burlington, NC.

2. REJECTIONS UNDER 35 USC §112, SECOND PARAGRAPH

Claims 1-12 were rejected under 35 USC §112, second paragraph, for indefiniteness. Such rejections have been overcome as follows.

Claim 1 has been amended to recite that the test article is "for performing dry reagent prothrombin time assays." Claim 1 has been further amended to recite that the solid phase is a "matrix."

Claim 5 has been amended to identify the coagulation neutral agents as those "which facilitate liquid sample uptake. . . ." Claim 5 has been further amended to recite "indicator face" on the penultimate line, rather than indicator faced.

The antecedent basis in claim 9 has been corrected.

Finally, claim 12 has been amended to conform the preamble to independent claim 9 and to clarify that the coagulation neutral agent is present when the dry thromboplastin is contacted with the sample.

A

Applicants believe that the above amendments clearly overcome the rejections stated under 35 USC §112, second paragraph.

3. REJECTIONS UNDER 35 USC §112, FIRST PARAGRAPH

Claims 1-12 were rejected under 35 USC §112, first paragraph, for lack of enablement. In particular, the Examiner argues that the claims fail to enable the phrases "coagulation neutral agents" and "proteins, water soluble polymers, and surfactants." The Examiner further argues that "undue experimentation" would be required to determine which substances would work in the instant invention." Such rejections are respectfully traversed.

The phrase "coagulation neutral agents" is clearly defined in the specification as embracing those substances which "enhance the uptake of liquid sample into the solid phase while displaying little or no effect on the measured prothrombin." As noted by the Examiner, the specification goes further and identifies a number of particular agents which are useful, including "proteins, such as bovine serum albumin; polymers, such as hydroxylpropyl cellulose, gantrez, polyvinyl alcohol, and polyethylene glycol; sugars, such as glucose and trehalose; polysaccharides, such as starch and dextrans; and surfactants, such as polyoxyethylene ethers." With such teachings, and with such specific identification of suitable materials, one skilled in the art would not be required to perform undue experimentation to determine which substances would work.

While the Examiner is correct that only two of exemplary substances are actually included in the working examples, there is no requirement that an application include any working examples. While the Examiner is also correct that chemical and biotechnological arts can be unpredictable, the identification of surface active agents which can enhance wetability of a membrane without adversely affecting a measured prothrombin time is well within the skill of one ordinarily skilled in the art. This is not a question of identifying substances having rare biological activities, it is rather the

simple task of making sure that the surface active agent employed will not have an adverse effect on the test being performed.

The phrase "proteins, water soluble polymers, and surfactants" is believed to be similarly enabled. The description on page 13 provides particular examples for each of these categories. Moreover, one skilled in the art would have absolutely no difficulty in identifying additional members of each category which are suitable as surface active agents in the present invention. As suggested by the Examiner, however, Applicants have amended claims 4, 8, and 12, to recite albumins in place of proteins.

In view of these remarks, it is respectfully requested that the rejections under 35 USC §112, first paragraph be withdrawn.

4. REJECTIONS OVER THE PRIOR ART

Claims 1-12 were rejected under 35 USC §103 as being unpatentable over the combination Bartl et al. in view of Terminiello et al., further in view of either Hawkins et al. or Tripodi et al. Such rejections are traversed in part and overcome in part.

The present invention comprises unique test articles for performing dry reagent prothrombin time assays having two particular characteristics. First, the test articles include solid phase membranes having coagulation neutral agents to facilitate rehydration of dry thromboplastin when a blood or plasma sample is applied to the membrane. Second, the dry thromboplastin is free from substances which interfere with the performance of the assay when blood or plasma is added to the dry thromboplastin. Surprisingly, Applicants herein have found that use of conventional coagulation neutral agents in dry prothrombin time assays together with purified thromboplastins, such as thromboplastin purified from bovine brain extract (the most common commercial type of thromboplastin) results in the occurrence of aberrant forms of thromboplastin which interfere with the test results. By employing thromboplastin sources free from such interfering substances, Applicants have found that

rehydration of dry thromboplastin can be achieved without the production of the aberrant test result.

The Bartl et al. patent is relevant in that it teaches a test article comprising a membrane having dry thromboplastin immobilized therein. Nowhere, however, does Bartl et al. teach that dry thromboplastin be "substantially free from substances which cause aberrant functioning intermediate transition states as the thromboplastin is rehydrated." Nor does Bartl et al. suggest that the solid phase membrane contain "coagulation neutral agents which facilitate rehydration of the thromboplastin." Perhaps because of its structure, the Bartl et al. device apparently does not require coagulation neutral agents to facilitate rehydration. It is noted that the sample is introduced first to an application matrix 3 and flows down a transport fleece 5 before being transferred to a separate reagent layer 7 containing the thromboplastin. This difference in structure may obviate the need recognized in the present invention to employ thromboplastin free from substances which cause aberrant functioning intermediate transition states. In any event, Bartl et al. does not suggest any reason why it would be desirable to provide a rehydration agent of any sort.

The Examiner relies on Terminiello et al. to suggest the use of rehydration agents in the test article of Bartl et al. Such reliance is unwarranted. While Terminiello et al. does teach the use of surfactants in dry agent assay devices, there is no suggestion that such agents would find particular use in test articles comprising dry thromboplastin. Indeed, the teaching of Bartl et al. is that such surfactants are not necessary. In the present invention, however, it has been found that the coagulation neutral agents are necessary in many instances in order to obtain adequate rehydration and distribution of sample to the matrix. The presence of such coagulation neutral agents, however, has been found by the inventors herein to cause aberrations in the performance of thromboplastin when the thromboplastin has been rehydrated in the presence of sample. The inventors have been able to overcome this problem, however, by utilizing particular thromboplastins, as defined in the

present specification, which are free from the substances associated with many thromboplastins and which cause the aberrant functioning intermediate transition states.

In particular, it has been found that recombinant thromboplastins, as set forth in claims 3, 7, and 11 are free from the interfering substances. The Examiner relies on the teachings of Hawkins or Tripodi as suggesting the use of such recombinant thromboplastins. Such reliance, however, is misplaced. Both Hawkins and Tripodi teach the use of recombinant thromboplastin in liquid phase systems. Based on these teachings, there would have been no reason to suspect that the use of dry thromboplastin from recombinant sources would have particular advantages when employed together with a coagulation neutral agent in a solid phase matrix of a test article for performing dry reagent prothrombin time assays.

In summary, the rejections stated under 35 USC §103 for obviousness must fail. None of the art relied on by the Examiner recognizes the unique problem which arises when thromboplastin preparations, such as those found in thromboplastin purified from brain extract, are incorporated into solid phase matrices and membranes together with coagulation neutral rehydration agents. Absent such teachings, there would have been no motivation to employ such purified thromboplastin together with coagulation neutral agents in test articles, of the type taught by Bartl et al.

In an effort to expedite prosecution of the present application, Applicants have amended independent claims 1, 5 and 9 to recite with more particularity that the aberrant functioning substances are those found in thromboplastin purified from brain extract.

In view of the above amendments and remarks, Applicants believe that all claims are now in condition for allowance and request that the application be passed to issue at an early date.

If for any reason the Examiner believes that a telephone conference would in any way expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at (415) 326-2400.

Respectfully submitted,

James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND KHOURIE and CREW
One Market Plaza
Steuart Street Tower, 20th Floor
San Francisco, California 94105

(415) 326-2400

JMH:kz:kk

H:\HOME\KAK\JMH\15381\15381-3.AMD